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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: KUDLA, Joseph S.
KAREN JACKSON	)	
	:	Group Art Unit: 1611
Application No.: 10/752,411	)	
	:	Confirmation No.: 4891
Filed: January 7, 2004	)	
	:	
For: METHOD FOR TREATMENT WITH A MONOPHASIC PHARMACEUTICAL COMPOSITION COMPRISING DEVAZEPIDE	)	July 28, 2008

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF PRIORITY DOCUMENT

Sir:

To perfect a claim to priority under 35 USC § 119 (a)-(d) in the above-identified application, Applicant submits herewith a certified copy of the following priority document:

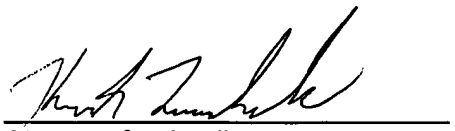
UK 0201367.0 filed on January 22, 2002

The priority document is referenced in a concurrently submitted amendment for the above-identified application. The priority document is in English and therefore no translation is necessary.

Applicants' attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

KATTEN MUCHIN ROSENMAN, LLP



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Intellectual Property Office
and Innovation

10752411

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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with patent application GB0201367.0 filed on 22 January 2002.

accordance with the Patents (Companies Re-registration) Rules 1982, if a company named this certificate and any accompanying documents has re-registered under the Companies 1980 with the same name as that with which it was registered immediately before re-stration save for the substitution as, or inclusion as, the last part of the name of the words "ic limited company" or their equivalents in Welsh, references to the name of the co any in this certificate and any accompanying documents shall be treated as references to the me with which it is so re-registered.

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Signed William Morell

Dated 7 May 2008

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P01/7700 0.00-0201367.0

Request for grant of a patent

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The Patent Office
Cardiff Road
Newport
South Wales
NP9 1RH

22 JAN 2002

1. Your reference

SPG/P36727

2. Patent application number
(The Patent Office will fill in this part)

0201367.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ML Laboratories Plc
17 Hanover Square
London
W1R 9AJ

Patents ADP number *(if you know it)*

7115280005

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Composition

5. Name of your agent *(if you have one)*

Harrison Goddard Foote

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

31 St Saviourgate
YORK
YO1 8NQ

7914237002

Patents ADP number *(if you know it)*

~~14571001~~

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	8
Claim(s)	7
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature S.P. Gilholm Date 22 January 2002

12. Name and daytime telephone number of person to contact in the United Kingdom S P Gilholm 01904 732120

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

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a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

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Composition

This invention relates to a novel pharmaceutical composition and to a novel method of treatment related thereto.

International Patent Application No. WO 99/18967 describes pharmaceutical compositions for treating chronic and neuropathic pain which comprises an analgesic amount of an opioid and an opioid potentiating amount of a CCK antagonist. WO '967 describes the use of both CCK-A antagonists and CCK-B antagonists, although it is described that, generally, CCK-B antagonists are preferred. Moreover, page 2, lines 6 to 8 of WO '967 describes that CCK-A antagonists may be suitable, but only at relatively higher dosages.

One specific CCK-A antagonist which is mentioned in WO 99/18967 is devazepide (Devacade®), which is 3s-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Devazepide is commonly administered alongside an opioid analgesic, e.g. such as morphine. However, in normal doses, the commonest side-effects of morphine and other opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance generally develops with long-term use, but not to constipation which is the most common undesirable side effect of morphine treatment.

International Patent Application No. WO 99/18967 specifically describes a pharmaceutical formulation comprising a CCK antagonist, such as devazepide, an opioid and a biphasic carrier, comprising a glyceride derivative organic phase. This application suggests the possible use of a surfactant, especially when the formulation is in the form of an oil-in-water emulsion.

We have now surprisingly found that a solid dosage form of devazepide may be prepared with a surfactant. The use of a surfactant is advantageous in that, *inter alia*,

it improves the powder flow and/or separation properties of solid devazepide and also reduces or mitigates the undesirable side effects of opioid administration, e.g. constipation.

Thus, according to the invention we provide a solid dosage pharmaceutical composition comprising a therapeutically effective amount of devazepide and a pharmaceutically acceptable surfactant.

We have found that the use of a surfactant in a solid dose devazepide composition has the advantage of mitigating constipation due to the concomitant administration of an opioid analgesic, whilst also improving the physical properties of devazepide in a solid dose formulation.

Any conventionally known pharmaceutically acceptable surfactants may be used in the composition of the invention. Such surfactants include, but shall not be limited to, a lipophilic surfactant, a hydrophilic surfactant or a glyceride, or combinations thereof.

When the surfactant is a hydrophilic surfactant, it may be an ionic or a non-ionic surfactant. Examples of non-ionic hydrophilic surfactants include, *inter alia*, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; tocopherol polyethylene glycol succinates; sugar esters; sugar ethers; sucroglycerides; and mixtures thereof.

Examples of ionic hydrophilic surfactants include, *inter alia*, alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, carnitines, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-, diacetylated tartaric acid esters of mono-, diglycerides; succinoylated monoglycerides; citric acid esters of mono-, diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulphates; salts of fatty acids; sodium docusate; and mixtures thereof.

Examples of lipophilic surfactants include, *inter alia*, alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

Examples of glycerides include mono-, di- or tri-glycerides. Such triglycerides include, *inter alia*, vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, synthetic triglycerides, modified triglycerides, fractionated triglycerides, and mixtures thereof.

In an especially preferred embodiment of the invention the surfactant will be capable of improving powder flow of devazepide and also be known to be a therapeutically effective laxative and/or stool softener. Such laxatives and/or stool softeners may,

preferentially be ionic surfactants, especially alkyl sulphosuccinates, alkyl sulphates or alkyl ammonium salts.

Thus, in a preferred embodiment of the invention the surfactant may be selected from the group, docusate sodium (dioctyl sodium sulphosuccinate), sodium dodecyl sulphate and tetradecyltrimethyl ammonium bromide.

In a further embodiment of the invention the surfactant may also possess antimicrobial and/or antiseptic properties. Thus, for example, when the surfactant is tetradecyltrimethylammonium bromide, it may, preferentially, be cetrimide (cetrimide is a mixture substantially comprising tetradecyltrimethyl ammonium bromide and small amounts of dodecyltrimethylammonium bromide and cetrimonium bromide).

In the most preferred embodiment of the invention the surfactant is docusate sodium.

The composition of the invention may preferentially comprise one or more fillers. Thus, such fillers may be selected from the group lactose, mannitol, talc, magnesium stearate, sodium chloride, potassium chloride, citric acid, spray-dried lactose, hydrolysed starches, directly compressible starch, microcrystalline cellulose, cellulosics, sorbitol, sucrose, sucrose-based materials, calcium sulphate, dibasic calcium phosphate and dextrose. A preferred filler is starch, e.g. corn starch.

When the composition of the invention includes a filler, the size of the devazepide and filler particles may be the same or different. However, in a preferred embodiment the sizes of the devazepide and filler particles will differ. Preferentially, the devazepide, surfactant and/or the filler may be of reduced particle size, e.g. by milling.

The devazepide, surfactant and filler may be present as an intimate mixture. However, in a preferred embodiment the filler particles may be coated with the

surfactant, the coated filler and devazepide then being formed into an intimate mixture.

Such compositions, comprising devazepide, a filler and a surfactant are especially advantageous in that, *inter alia*, the surfactant acts to hinder or prevent separation of the devazepide and the filler, whilst also providing the desirable laxative and/or stool softening properties as hereinbefore described.

The amount of surfactant present in the composition of the invention may vary, depending upon, *inter alia*, the level of devazepide present, the level of concomitant opioid analgesic administered, etc. Generally, the ratio of devazepide:surfactant may be from 5:1 to 25:1 w/w, preferably from 10:1 to 15:1 w/w, most preferably 12.5:1 w/w.

When the composition of the invention includes a filler, the composition may generally comprise devazepide and a surfactant, in the ratio as hereinbefore described, with the remainder of the composition being made up with a filler.

A preferred embodiment of the invention comprises a formulation as hereinbefore described filled into a capsule. Any conventionally known materials may be used for the capsule, however a preferred material is gelatin.

Thus, for example, in one embodiment of the invention the composition may be made up into a capsule formulation, e.g. with a fill weight of 150 mg ± 5% by weight or 300 mg ± 5% by weight. In the one preferred embodiment, the capsule formulation may comprise 1.25mg devazepide, 0.1 mg surfactant, e.g. docusate sodium, and 148.65 mg of a filler, e.g. corn starch. In a further preferred embodiment, the capsule formulation may comprise 2.5mg devazepide, 0.2 mg surfactant, e.g. docusate sodium, and 297.3 mg of a filler, e.g. corn starch.

According to a further aspect of the invention we provide a method of treatment of a patient undergoing opioid analgesic therapy which comprises the administration of a pharmaceutical composition as hereinbefore described.

According to a yet further aspect of the invention we provide a method of treatment of a patient requiring analgesia which comprises the separate, simultaneous or sequential administration of a therapeutically effective amount of an opioid analgesic, devazepide and a surfactant/stool softener.

In the method of the invention a variety of opioids may be used. Thus, the opioid may be selected from those which are effective analgesics and particularly those which need to be administered at relatively high or increasing doses. Examples include morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or the other 1,4-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine, fentanyl, alfentanil, alphaprodine, buprenorphine, dextromoramide, diphenoxylate, dipipanone, heroin (diacetylmorphine), hydrocodone (dihydrocodeinone), hydromorphone (dihydromorphinone), levorphanol, meptazinol, methadone, metopon (methyldihydromorphinone), nalbuphine, oxycodone (dihydrohydroxycodeinone), oxymorphone (dihydrohydroxymorphinone), phenadoxone, phenazocine, remifentanil, tramadol, or a salt of any of these. Especially preferred analgesics which may be mentioned are hydromorphone, oxycodone, morphine, e.g. morphine sulphate and fentanyl. In a preferred embodiment of the invention the analgesic is morphine or morphine sulphate.

In the method of the invention the devazepide and/or the opioid may be administered using any methods conventionally known *per se*. Thus, such methods would include, but shall not be limited to, administration intravenously, orally, intrathecally, intranasally, intrarectally, intramuscularly/subcutaneously, by inhalation and by transdermal patch. Preferably, the opioid and/or devazepide are administered orally.

Preferentially, when the opioid and the devazepide will be administered using the same mode of administration. Thus, for example, when the opioid is administered orally then the devazepide may be administered orally also. However, it is within the scope of the invention for the opioid to be administered intravenously and the devazepide to be administered orally.

Thus, in the method of the invention the daily dosage of devazepide may vary depending upon, *inter alia*, the weight of the patient, the method of administration, etc. In patients that are suffering serious disorders, such as cancer patients, the weight of the patient may be very low and therefore the dosage of devazepide consequentially may be low. Thus the daily dosage of devazepide may be up to 0.7 mg/kg/day. Preferably, the daily dosage of devazepide may be from 25 µg/kg/day to 0.7 mg/kg/day, more preferably from 50 µg/kg/day to 0.5 mg/kg/day. For oral administration the daily dosage of devazepide may be from preferably 0.07 mg/kg/day to 0.29 mg/kg/day. For intravenous administration the dosage of devazepide is preferably 50 µg/kg/day to 0.5 mg/kg/day.

Thus, the expected daily dose of laxative/stool softener may be from 0.4mg to 1.6mg, preferably 0.8mg.

In the method of the invention the dosage of the opioid analgesic administered may vary depending upon, inter alia, the nature of the opioid analgesic, the weight of the patient, the method of administration, etc. Thus, for example, the dosage of, e.g. an opioid, such as morphine, may be from 5 to 2000mg daily. A particular dosage which may be mentioned is from 10 to 240mg daily. A daily dosage of morphine may be from 5 to 100mg or occasionally up to 500mg.

According to a further aspect of the invention we provide the use of devazepide in the manufacture of a pharmaceutical composition as hereinbefore described.

The devazepide used in the method and/or the composition of the invention is the S enantiomer, preferentially, the S enantiomer wherein the level of R enantiomer, which may be present as an impurity, is not greater than 1.5% w/w.

CLAIMS

1. A solid dosage pharmaceutical composition comprising a therapeutically effective amount of devazepide and a pharmaceutically acceptable surfactant.

2. A pharmaceutical composition according to Claim 1 characterised in that the surfactant is a lipophilic surfactant, a hydrophilic or a glyceride, or combinations thereof.

3. A pharmaceutical composition according to Claim 2 characterised in that the surfactant is a hydrophilic surfactant.

4. A pharmaceutical composition according to Claim 3 characterised in that the hydrophilic surfactant is an ionic or a non-ionic surfactant.

5. A pharmaceutical composition according to Claim 4 characterised in that the hydrophilic surfactant is a non-ionic surfactant selected from the group alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; tocopherol polyethylene glycol succinates; sugar esters; sugar ethers; sucroglycerides; and mixtures thereof.

6. A pharmaceutical composition according to Claim 4 characterised in that the hydrophilic surfactant is an ionic surfactant selected from the group alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of

amino acids, carnitines, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-, diacetylated tartaric acid esters of mono-, diglycerides; succinoylated monoglycerides; citric acid esters of mono-, diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulphates; salts of fatty acids; docusate sodium; and mixtures thereof.

7. A pharmaceutical composition according to Claim 2 characterised in that the surfactant is a lipophilic surfactant.

8. A pharmaceutical composition according to Claim 7 characterised in that the lipophilic surfactant is selected from the group alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

9. A pharmaceutical composition according to Claim 8 characterised in that the surfactant is a glyceride.

10. A pharmaceutical composition according to Claim 9 characterised in that the triglyceride is selected from the group vegetable oils, fish oils, animal fats,

hydrogenated vegetable oils, partially hydrogenated vegetable oils, synthetic triglycerides, modified triglycerides, fractionated triglycerides, and mixtures thereof.

11. A pharmaceutical composition according to Claim 1 characterised in that the surfactant is a therapeutically effective laxative and/or stool softener.

12. A pharmaceutical composition according to Claim 11 characterised in that the surfactant is selected from the group alkyl sulphosuccinates, alkyl sulphates or alkyl ammonium salts.

13. A pharmaceutical composition according to Claim 12 characterised in that the surfactant is selected from the group, docusate sodium (dioctyl sodium sulphosuccinate), sodium dodecyl sulphate and tetradecyltrimethyl ammonium bromide.

14. A pharmaceutical composition according to Claim 1 characterised in that the surfactant also possesses antimicrobial and/or antiseptic propertics.

15. A pharmaceutical composition according to Claim 1 characterised in that the surfactant is cetrimide.

16. A pharmaceutical composition according to Claim 14 characterised in that the surfactant is docusate sodium.

17. A pharmaceutical composition according to Claim 1 characterised in that the composition comprises one or more fillers.

18. A pharmaceutical composition according to Claim 17 characterised in that the filler particles are coated with the surfactant, the coated filler and devazepide then being formed into an intimate mixture.

19. A pharmaceutical composition according to Claim 17 characterised in that the filler is selected from the group lactose, mannitol, talc, magnesium stearate, sodium chloride, potassium chloride, citric acid, spray-dried lactose, hydrolysed starches, directly compressible starch, microcrystalline cellulose, cellulosics, sorbitol, sucrose, sucrose-based materials, calcium sulphate, dibasic calcium phosphate and dextrose and mixtures thereof.

20. A pharmaceutical composition according to Claim 19 characterised in that the filler is starch.

21. A pharmaceutical composition according to Claim 20 characterised in that the starch is corn starch.

22. A pharmaceutical composition according to Claim 17 characterised in that the size of the devazepide particles and the filler particles are different.

23. A pharmaceutical composition according to Claim 1 characterised in that the ratio of devazepide:surfactant is from 5:1 to 25:1 w/w.

24. A pharmaceutical composition according to Claim 17 characterised in that the composition comprises devazepide and a surfactant with the remainder of the composition being made up with a filler.

25. A pharmaceutical composition according to Claim 17 characterised in that the composition comprises 1.25mg devazepide, 0.1 mg surfactant and 148.65 mg of a filler.

26. A pharmaceutical composition according to Claim 25 characterised in that the composition comprises 1.25mg devazepide, 0.1 mg docusate sodium and 148.65 mg of corn starch.

27. A pharmaceutical composition according to Claim 17 characterised in that the composition comprises is 2.5mg devazepide, 0.2 mg surfactant and 297.3mg of a filler.

28. A pharmaceutical composition according to Claim 27 characterised in that the composition comprises 2.5mg devazepide, 0.2mg docusate sodium and 297.3mg corn starch.

29. A pharmaceutical composition according to Claim 1 characterised in that the formulation is in a gelatin capsule.

30. A method of treatment of a patient undergoing opioid analgesic therapy which comprises the administration of a pharmaceutical composition according to claim 1.

31. A method of treatment of a patient requiring analgesia which comprises the separate, simultaneous or sequential administration of a therapeutically effective amount of an opioid analgesic, devazepide and a surfactant/stool softener.

32. A method of treatment according to claim 31 characterised in that the devazepide and surfactant/stool softener are presented as a composition according to claim 1.

33. A pharmaceutical composition according to Claim 1 characterised in that the opioid is selected from the group morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or the other 1,4-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine, fentanyl, alfentanil, alphaprodine, buprenorphine, dextromoramide, diphenoxylate, dipipanone, heroin (diacetylmorphine), hydrocodone (dihydrocodeinone), hydromorphone (dihydromorphinone), levorphanol, meptazinol, methadone, metopon (methyldihydromorphinone), nalbuphine, oxycodone (dihydrohydroxycodeinone),

oxymorphone (dihydrohydroxymorphinone), phenadoxone, phenazocine, remifentanil, tramadol, or a salt of any of these.

34. A pharmaceutical composition according to Claim 33 characterised in that the opioid is selected from the group hydromorphone, oxycodone, morphine and fentanyl.

35. A pharmaceutical composition according to Claim 34 characterised in that the opioid is morphine or morphine sulphate.

36. A method according to Claim 30 characterised in that the daily dosage of devazepide is up to 0.7 mg/kg/day.

37. A method according to Claim 36 characterised in that the daily dosage of devazepide is from 25 µg/kg/day to 0.7 mg/kg/day.

38. A method according to Claim 37 characterised in that the daily dosage of devazepide is from 50 µg/kg/day to 0.5 mg/kg/day.

39. A method according to Claim 36 characterised in that for oral administration the daily dosage of devazepide is from 0.07 mg/kg/day to 0.29 mg/kg/day.

40. A method according to Claim 36 characterised in that for intravenous administration the dosage of devazepide is 50 µg/kg/day to 0.5 mg/kg/day.

41. A method according to Claim 31 characterised in that the daily dose of laxative/stool softener is from 0.4mg to 1.6mg per day.

42. A method according to Claim 31 characterised in that the dosage of an opioid is from 5 to 2000mg daily.

43. A method according to Claim 42 characterised in that the dosage of the opioid is from 10 to 240mg daily.

44. A method according to Claim 30 characterised in that the devazepide used is the S enantiomer, wherein the level of R enantiomer, which may be present as an impurity, is not greater than 1.5% w/w.

45. The use of devazepide in the manufacture of a pharmaceutical composition according to claim 1.

46. A composition or a method substantially as described with reference to the accompanying examples.

P36727.3